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Intake of High-Fat Yogurt, but Not of Low-Fat Yogurt or Prebiotics, Is Related to Lower Risk of Depression in Women of the SUN Cohort Study[1–3]

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Abstract

Background: Yogurt and prebiotic consumption has been linked to better health. However, to our knowledge, no longitudinal study has assessed the association of yogurt and prebiotic consumption with depression risk.

Objective: We longitudinally evaluated the association of yogurt and prebiotic consumption with depression risk in a Mediterranean cohort.

Methods: The SUN (Seguimiento Universidad de Navarra) Project is a dynamic, prospective cohort of Spanish university graduates. A total of 14,539 men and women (mean age: 37 y) initially free of depression were assessed during a median follow-up period of 9.3 y. Validated food-frequency questionnaires at baseline and after a 10-y follow-up were used to assess prebiotic (fructans and galacto-oligosaccharide) intake and yogurt consumption (<0.5, ≥0.5 to <3, ≥3 to <7, and ≥7 servings/wk). Participants were classified as incident cases of depression when they reported a new clinical diagnosis of depression by a physician (previously validated). Multivariable Cox proportional hazards models were used to calculate HRs and 95% CIs.

Results: We identified 727 incident cases of depression during follow-up. Whole-fat yogurt intake was associated with reduced depression risk: HR for the highest [≥7 servings/wk (1 serving = 125 g)] compared with the lowest (<0.5 servings/wk) consumption: 0.78 (95% CI: 0.63, 0.98; *P*-trend = 0.020). When stratified by sex, this association was significant only in women (HR: 0.66; 95% CI: 0.50, 0.87; *P*-trend = 0.004). Low-fat yogurt consumption was associated with a higher incidence of depression (HR: 1.32; 95% CI: 1.06, 1.65; *P*-trend = 0.001), although this association lost significance after the exclusion of early incident cases, suggesting possible reverse causation bias. Prebiotic consumption was not significantly associated with depression risk.

Conclusions: Our study suggests that high consumption of whole-fat yogurt was related to a lower risk of depression in women of the SUN cohort. No association was observed for prebiotics. Further studies are needed to clarify why the yogurt-depression association may differ by fat content of the yogurt. *J Nutr* 2016;146:1731–9.

Keywords: depression, yogurt, prebiotics, fiber, probiotics

Introduction

Unipolar depression has reached epidemic proportions worldwide and is expected to be the leading cause of disability in developing countries by the year 2030 (1). Although depression seems to be a multifactorial disease (2), diet has recently emerged as a determinant factor for the prevention and treatment of this mental disorder (3). Current studies have shown that diet influences gut microbiota composition and activity (4), and that this, in turn, may influence brain function, including depressive illness (5, 6). Some of the mechanisms that may link these functions include immune, neural, and metabolic pathways (5). Therefore, the gut microbiota–brain axis has been proposed as an underlying link between diet quality and depression (6).

Both probiotics and prebiotics are able to enhance and maintain a healthy gut microbiota in humans (7). Probiotics are defined as "live microorganisms that, when administered in

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adequate amounts, confer a health benefit on the host" (8). Probiotics must survive the gastrointestinal transit to exert a health-promoting effect (9), and they can be consumed in various forms, but mainly as either a functional food, such as in yogurt/fermented milk formulas with live probiotic bacteria, or as encapsulated supplements. Probiotic bacteria such as *Bifidobacterium bifidum* and/or *Lactobacillus acidophilus* can be added to yogurts and fermented milks (8), and there is currently a wide range of yogurts and fermented milks on the market that contain probiotic bacteria (10). Commercial yogurt fulfills the current concept of probiotics if it contains viable, live, and abundant beneficial bacteria (namely *Streptococcus thermophilus* and *Lactobacillus bulgaricus*) at a minimum concentration of 10^7 CFUs/g (9). Above this concentration, several health benefits linked to the presence of live bacteria in yogurt have been observed (11). Commercial yogurt consumption has been suggested to favorably alter the gut microbiota and gut function (12), decrease the risk of overweight or obesity and metabolic syndrome (13, 14), improve immune-system activity (15), and lead to a better lipid profile (16). To date, the association between yogurt or fermented milks and depression has not been investigated; however, probiotic consumption was previously reported to be associated with reduced anxiety and depressive-like behaviors in some small-scale human studies (17).

A prebiotic is defined as "a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health" (18). Fructans [fructo-oligosaccharides (FOSs)[10] and inulin] and galacto-oligosaccharides (GOSs) are the most important prebiotic sources, and they are mostly present in fruit, vegetables and whole grains (19). Among the beneficial effects attributed to prebiotics are the intestinal growth of beneficial bacteria (e.g., *Bifidobacterium* and/or *Lactobacillus* strains), the improvement of gut barrier function and host immunity, a lower risk of overweight or obesity, and mitigation of inflammatory responses (20–22). Moreover, prebiotic administration may have antidepressant effects by modulating the hypothalamic-pituitary-adrenal axis, the immune system, and metabolite-mediated pathways (5).

Considering that the suggested beneficial effects of probiotics and prebiotics on brain development and behavior through the gut microbiota–brain axis are mainly based on animal studies and small short-term human studies (5, 6), it is of great interest to determine whether the consumption of prebiotics and yogurt or fermented milks is associated with a reduced risk of depression in the long term in a large human study. Therefore, our aim was to prospectively assess the association of yogurt (total, whole-fat, and low-fat) and prebiotic consumption with the incidence of depression among university graduates enrolled in a longitudinal study with an average follow-up period >9 y, the Seguimiento Universidad de Navarra (SUN) Project.

Methods

Study population. The SUN study is a prospective cohort study with continually open recruitment (i.e., a dynamic design), started in December 1999 with alumni of the University of Navarra, registered professionals from some Spanish provinces, and other university graduates. Detailed information on this cohort has been described elsewhere (23). Briefly, at enrollment and every 2 y, self-reported questionnaires are administered to collect and update medical and lifestyle information, although dietary information was collected only twice, at baseline and after 10 y of follow-up.

For the present analysis, we included 21,291 participants who had answered the baseline questionnaire before March 2012 to ensure that all participants had the opportunity to answer the 2-y follow-up questionnaire. Participants who reported total energy intakes at baseline outside of recommended limits (total energy intakes >4000 and >3500 kcal/d in men and women, respectively, and intakes <800 kcal/d in men and <500 kcal/d in women; n = 2011) were not included in the analysis (24). Participants with cancer, diabetes, or cardiovascular disease at the beginning of the study were also excluded (n = 1198). We excluded 2085 participants who reported antidepressant medication at baseline or who had a history of physician-diagnosed depression throughout their life. Of the 16,000 remaining participants, 1427 subjects were lost to follow-up (retention rate: 91%), and 31 participants had missing data on some of the variables of interest. Finally, data from 14,539 participants were included in our main longitudinal analysis.

This study was conducted according to the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of the University of Navarra. The completion of the self-administered questionnaire was considered to imply informed consent (23).

Assessment of prebiotic and yogurt consumption. Dietary intake was measured by a self-administered 136-item semiquantitative FFQ administered twice, at baseline and after 10 y of follow-up, which has been previously validated in Spain (25). The FFQ used in this study was not focused on each individual food but on food groups. The intraclass correlation coefficient for dairy products from the FFQ and from four 3-d food records was 0.84 (26). To determine usual dietary intake over the previous year, frequencies of intake were measured in 9 categories, ranging from "never or almost never" to "six or more times per day."

As previously detailed (22), we used dietary intakes from the FFQ to calculate the total fructans (FOSs and inulin) and GOS consumption, and these values were updated in 29% of participants who completed the 10-y follow-up FFQ. This percentage is not high, largely because of the late entry in the cohort and its dynamic design. Total prebiotic consumption was estimated by summing total fructans and GOS consumption. The main food contributors to fructans and GOS intakes in our cohort were vegetables (the main contributor was asparagus) and cereals (the main contributors were both white bread and whole-grain bread) (22).

Participants reported the frequency of whole-fat and low-fat yogurt consumption in both FFQs (at baseline and after 10 y of follow-up), whereas total yogurt consumption was calculated by summing the previous 2 food items. Participants were allocated into 4 categories according to servings (1 serving = 125 g) of yogurt (total, whole-fat [~3% fat], and low-fat (~0.1% fat)] consumed per week: <0.5 servings (<63 g), ≥0.5 to <3 servings (≥63 to <250 g), ≥3 to <7 servings (≥250 to <875 g), and ≥7 servings (≥875 g).

Outcome assessment. Information on physician-diagnosed depression is updated biennially (Q_2-Q_14). Thus, we defined as an incident case of depression any participant who responded affirmatively to the question "Have you ever been diagnosed with depression by a medical doctor?" and who was free of depression at baseline. Self-reported medical diagnosis of depression has been previously validated in a subsample of this cohort by using the Structured Clinical Interview for

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[3] Supplemental Tables 1 and 2 are available from the ''Online Supporting Material'' link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
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[10] Abbreviations used: FOS, fructo-oligosaccharide; GOS, galacto-oligosaccharide; MedDiet, Mediterranean diet; SUN, Seguimiento Universidad de Navarra.

the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, as the gold standard (27). The percentage of confirmed depression cases was 74.2% (95% CI: 63.3%, 85.1%) and the percentage of confirmed nondepression cases was 81.1% (95% CI: 69.1%, 92.9%).

Assessment of covariates. Demographic characteristics (e.g., age, sex, and marital and employment status), lifestyle behaviors [e.g., smoking status, leisure-time physical activity, total energy intake, adherence to the Mediterranean diet (MedDiet) by using the MedDiet score proposed by Bach et al. (28), and fiber consumption], weight gain (>3 kg) in the 5 y before entering the cohort, BMI, and comorbidity information (e.g., prevalence/history of cancer, diabetes, or cardiovascular disease) were collected in the baseline questionnaire. Participants also answered questions about personality and behavior, such as their levels of competitiveness, anxiety, and dependence, by using Likert scales with values in the range of 0–10. Finally, physical activity was assessed with a validated questionnaire (29).

Statistical analysis. Chi-square tests for trend (categorical variables) and ordinary least-squares linear regression analyses (continuous variables) across categories or prebiotic and yogurt consumption were used for comparisons of baseline characteristics. We categorized our exposure variables in quartiles, because quartiles allow for a sufficiently high (and equally sized) sample size in each category and for assessment of dose-response trends.

Cox regression models were fitted to assess the relation of yogurt and prebiotic consumption at baseline with the risk of developing depression during follow-up, at which time HRs (95% CIs) were calculated. Tests for linear trend across quartiles of yogurt or prebiotic consumption were performed by assigning the median value of intake within each category and treating these as continuous variables in the respective multivariable-adjusted Cox regression models. Prebiotic and yogurt consumption data were updated after 10 y of follow-up, and Cox regression models with time-dependent exposures were also fitted. Age was used as the underlying time variable. Age at baseline was used as the entry time variable. Birth date was taken as the origin of the time scale. Exit time was defined as a diagnosis of depression or age at censoring due to death or loss to follow-up. Analyses were stratified by date of recruitment (2-y periods) and deciles of age. The proportional hazards assumption was assessed by using the Schoenfeld residuals method.

In the multiple-adjusted models, the following potential confounders were included as covariates: age (underlying time variable), sex, smoking (never, current, former, or missing), physical activity (quartiles), total energy intake (quartiles), baseline BMI (quartiles), living alone (yes or no), unemployment (yes or no), marital status (married or not), and the 3 personality traits [competitiveness (higher scores, more competitive), relaxation (lower scores, more relaxed), and dependency or locus of control (higher scores, more dependent)]. Two a priori–defined tests for interaction by sex and age (≤40 or >40 y) were conducted by introducing interaction terms in the model and then comparing the models with and without the interaction term by using likelihood ratio tests. We conducted stratified analyses according to the fat content to explore potential differential associations because other studies have suggested a possible difference (30).

Finally, we performed sensitivity analyses to test the robustness of our estimates. We reconducted our analyses with the use of the following alternative assumptions: *1*) additionally adjusting for adherence to the MedDiet; *2*) additionally adjusting for other fiber consumption apart from prebiotics (only in the prebiotic analysis); *3*) additionally adjusting for n–3 PUFAs; *4*) excluding early incident cases of depression (until 2 y of follow-up); *5*) including prevalent cancer, diabetes, or cardiovascular disease; *6*) including only those participants with prevalent obesity [BMI (in kg/m^2) >30]; *7*) including only those participants who had gained ≥3 kg in the past 5 y; *8*) changing the energy limits (5th–95th percentiles); *9*) including only women and excluding early incident cases of depression (until 2 y of follow-up); and *10*) including only men and excluding early incident cases of depression (until 2 y of follow-up). The rationale for the exclusion of these early cases was that cases diagnosed early during the follow-up period might be more likely to have been present as subclinical cases at baseline. All of the analyses were 2-tailed, and $P < 0.05$ was considered significant. Statistical analyses were performed by using STATA version 12.0 (StataCorp).

Results

The characteristics of participants subdivided by categories of total prebiotic and yogurt consumption are shown in **Table 1**. The highest category of total prebiotic consumption included a higher proportion of women, nonsmokers, unemployed participants, and participants with better adherence to the MedDiet, who were more physically active, and with a lower BMI. There were higher proportions of women, nonsmokers, younger people, unemployed participants, and participants living alone among those in the highest category of total yogurt consumption. Moreover, participants with a higher yogurt consumption were more physically active and had better adherence to the MedDiet.

After 9.3 y of follow-up, a total of 727 incident cases of depression were identified. The exposure variables were all defined by using repeated measurements of diet (baseline and after 10 y of follow-up). No interaction was observed between age or sex and any of the dietary exposures (P-interaction = 0.12–0.90). However, there was a significant sex × low-fat yogurt intake interaction (P-interaction = 0.017), so these data are also presented for each sex separately.

The association between prebiotic consumption and the risk of depression is shown in **Table 2**. In all of the participants, the multiple-adjusted model showed that although a higher consumption of fructans, GOSs, and total prebiotics seemed to be associated with a lower risk of depression [HRs (95% CIs) for the highest compared with the lowest quartile of intake: 0.94 (0.74, 1.20) for fructans, 0.87 (0.69, 1.08) for GOSs, and 0.92 (0.73, 1.17) for total prebiotics], this association was not significant. When analyses were divided by sex, no association between prebiotic intake (fructans, GOSs, and total prebiotics) and depression risk was observed.

Table 3 shows the HRs for depression in relation to yogurt consumption. With consideration of all participants, whole-fat yogurt intake was associated with a decreased risk of depression [HR for the highest (≥7 servings/wk) compared with the lowest (<0.5 servings/wk) consumption: 0.78; 95% CI: 0.63, 0.98; P-trend = 0.020]. Conversely, a higher consumption of low-fat yogurt was related to a higher risk of depression [HR for the highest (≥7 servings/wk) compared with the lowest (<0.5 servings/wk) consumption: 1.32; 95% CI: 1.06, 1.65; P-trend = 0.001], but there was no evidence of an association with total yogurt intake. Stratified analyses showed that the previous associations between yogurt consumption and incident depression were only significant in women [HRs (95% CIs) for the highest (≥7 servings/wk) compared with the lowest (<0.5 servings/wk) consumption: 0.66 (0.50, 0.87; P-trend = 0.004) and 1.37 (1.07, 1.76; P-trend < 0.001) for whole-fat and low-fat yogurt, respectively].

The association between fructans, GOSs, and total prebiotic consumption and the incidence of depression remained nonsignificant in all of our sensitivity analyses (**Supplemental Table 1**), and no association between total yogurt consumption and the risk of depression was observed (**Supplemental Table 2**). When nonobese participants and those with a stable weight in the past 5 y were excluded, the inverse association between whole-fat yogurt consumption and the risk of depression was attenuated (Supplemental Table 2). However, excluding early incident cases of depression (until 2 y of follow-up); additionally adjusting for adherence to the MedDiet or n–3 PUFAs; including participants

with prevalent cancer, diabetes, or cardiovascular disease; and including those with energy limits between the 5th and 95th percentiles did not alter the results. In analyses stratified by sex we observed that the inverse association between whole-fat yogurt and depression risk in women remained statistically significant even after excluding early incident cases. Importantly, the positive association of low-fat yogurt consumption with the incidence of depression was no longer significant after excluding early cases of depression (Supplemental Table 2). This was observed in all of the participants and also in women.

Discussion

In this prospective study, we found that a higher consumption of whole-fat yogurt was related to a lower risk of depression in women. The consumption of prebiotics or total yogurt was not significantly associated with depression risk. These longitudinal results are novel, and this is, to our knowledge, the first prospective study that analyzed the association between yogurt and prebiotic consumption and depression risk.

Unhealthy diets have been shown to have a detrimental effect on depression due to their harmful effects on hormones, the immune system, neurodegenerative factors, and the expression of potentially damaging genes (31–35). Conversely, healthy dietary patterns, such as the MedDiet, the Alternative Healthy Eating Index, or a plant-based ("provegetarian") dietary pattern, might have a protective effect against the incidence of depression (36).

Recent evidence suggests that prebiotics, including fructans and GOSs, modulate brain function by modifying the gut microbiota, decreasing low-grade inflammation, and/or influencing the production of neurochemicals (5, 6). Prebiotics are fermented by beneficial bacteria, including *Bifidobacterium and Lactobacillus*, to produce SCFAs, which may suppress proinflammatory cytokines (37). A recent study in healthy volunteers showed that those supplemented with bimuno-GOSs had lower cortisol awakening reactivity (a reliable marker of hypothalamic-pituitary-adrenal axis activity), whereas FOS administration had no effect (38). An animal study showed that prebiotic feeding increased brain-derived neurotropic factor expression, probably through the involvement of gut hormones (39). The same authors also showed that the ingestion of bimuno-GOSs attenuated postinflammatory anxiety in mice (40). In the current study we did not find any significant association between prebiotic consumption and the risk of depression. However, the point estimates suggest that prebiotic consumption, especially GOSs, might be associated with a lower risk of depression; therefore, it would be of great interest to replicate these analyses in a cohort with a larger number of incident cases of depression to increase the statistical power.

A surprising finding of our study was a direct association between low-fat yogurt consumption and depression risk among women. However, this association was no longer significant after excluding those cases of depression that occurred within the first 2 y of follow-up. Therefore, this association might be due to reverse causality, so that subclinical

TABLE 1 Baseline characteristics of participants according to their total prebiotic and yogurt consumption: the SUN cohort, 1999–2012[1]

	Prebiotic consumption[2]					Total yogurt consumption[3]				
	Q1	Q2	Q3	Q4	*P*-trend[4]	<0.5 servings/wk	≥0.5 to <3 servings/wk	≥3 to <7 servings/wk	≥7 servings/wk	*P*-trend[4]
Median	1.1	1.8	2.4	3.4		0	1	3	7	
n	3635	3635	3635	3634		3133	1871	5489	4046	
Women, %	55.3	59.5	59.4	62.4	<0.001	51.2	56.5	59.6	65.8	<0.001
Age, y	37.8 ± 11.7	37.3 ± 11.4	37.4 ± 11.4	37.8 ± 11.9	0.99	41.2 ± 12.6	37.5 ± 11.3	36.2 ± 10.9	36.7 ± 11.26	<0.001
Baseline BMI, kg/m^2	23.7 ± 3.6	23.4 ± 3.4	23.4 ± 3.4	23.3 ± 3.3	<0.001	23.9 ± 3.6	23.6 ± 3.5	23.4 ± 3.4	23.2 ± 3.3	<0.001
Married, %	50.7	50.8	50.9	50.3	0.80	58.2	49.8	48.4	48.3	<0.001
Unemployed, %	4.0	4.5	3.9	3.8	<0.001	3.3	3.7	4.4	4.3	<0.001
Smoking status, %					<0.001					<0.001
Current smoker	26.5	21.7	21.0	18.4		27.9	25.9	21.2	16.4	
Former smoker	29.0	28.0	28.8	28.2		32.1	30.2	26.1	28.3	
Living alone, %	7.2	6.7	5.7	6.3	0.046	5.5	6.2	6.4	7.3	0.002
Physical activity, MET-h/wk	19.0 ± 20.6	21.0 ± 21.9	22.5 ± 22.3	24.6 ± 26.3	<0.001	19.6 ± 22.0	20.1 ± 21.1	21.8 ± 22.5	24.2 ± 24.8)	0.000
Weight gain >3 kg in the 5 y before entering the cohort, %	32.2	30.5	28.9	28.9	0.001	31.1	30.6	31.0	28.0	0.012
Total energy intake, kcal/d	1890 ± 526	2250 ± 505	2490 ± 516	2800 ± 522	<0.001	2220 ± 650	2300 ± 593	2360 ± 599	2480 ± 596	<0.001
Adherence to the Mediterranean dietary pattern (score of 0–9)	3.1 ± 1.6	3.9 ± 1.6	4.6 ± 1.7	5.2 ± 1.6	<0.001	4.3 ± 1.8	4.3 ± 1.8	4.1 ± 1.8	4.3 ± 1.8	<0.001
n–3 PUFAs, g/d	2.3 ± 1.2	2.6 ± 1.2	2.7 ± 1.2	2.9 ± 1.3	<0.001	2.5 ± 1.3	2.6 ± 1.1	2.6 ± 1.2	2.7 ± 1.3	<0.001
Total dietary fiber intake, g/d	18.5 ± 7.3	25.0 ± 7.8	28.9 ± 9.2	38.0 ± 13.2	<0.001	26.4 ± 12.8	25.9 ± 10.8	26.9 ± 11.1	30.2 ± 12.6	<0.001
Total prebiotic consumption,[2] g/d	1.1 ± 0.3	1.7 ± 0.2	2.4 ± 0.2	3.7 ± 1.0	<0.001	2.1 ± 1.2	2.1 ± 1.0	2.2 ± 1.1	2.4 ± 1.2	<0.001
Total yogurt intake, g/wk	493 ± 619	579 ± 632	592 ± 623	657 ± 707	<0.001	26 ± 31	147 ± 44	487 ± 151	1330 ± 756	<0.001

[1] Values are means ± SDs unless otherwise indicated. MET-h, metabolic equivalent task hours; Q, quartile; SUN, Seguimiento Universidad de Navarra.
[2] Sum of galacto-oligosaccharides and fructans.
[3] 1 serving = 125 g.
[4] *P* values were derived by using chi-square test for trend (categorical variables) and linear regression models (continuous variables) across categories of prebiotic and yogurt consumption.

TABLE 2 HRs (95% CIs) for incident depression (diagnosis of depression) according to intake of prebiotics in the SUN cohort (1999–2012) stratified by sex[1]

	Quartile				
	1	2	3	4	*P*-trend
Overall sample					
n	3635	3635	3635	3634	
Fructans					
Median, g/d	0.9	1.5	2.0	2.9	
Fructans, g/d	1.0 ± 0.2[2]	1.5 ± 0.1	2.0 ± 0.2	3.1 ± 0.9	
n cases/person-years	180/29,454	184/29,494	192/29,358	171/29,358	
Multiple-adjusted model	1.00 (ref)	1.04 (0.84, 1.29)	1.07 (0.86, 1.33)	0.94 (0.74, 1.20)	0.70
Galacto-oligosaccharides					
Median, g/d	0.1	0.2	0.4	0.5	
Galacto-oligosaccharides, g/d	0.1 ± 0.1	0.25 ± 0.1	0.4 ± 0.0	0.6 ± 0.2	
n cases/person-years	187/29,220	187/29,425	172/29,415	181/29,856	
Multiple-adjusted model	1.00 (ref)	0.97 (0.79, 1.19)	0.91 (0.74, 1.12)	0.87 (0.69, 1.08)	0.16
Total prebiotics[3]					
Median, g/d	1.1	1.8	2.4	3.4	
Total prebiotics, g/d	1.1 ± 0.3	1.8 ± 0.2	2.4 ± 0.2	3.6 ± 0.9	
n cases/person-years	182/29,537	193/29,443	173/29,523	179/29,412	
Multiple-adjusted model	1.00 (ref)	1.06 (0.86, 1.30)	0.94 (0.76, 1.18)	0.92 (0.73, 1.17)	0.34
Women					
n	2150	2150	2150	2149	
Fructans					
Median, g/d	1.0	1.5	2.0	3.0	
Fructans, g/d	0.9 ± 0.3	1.5 ± 0.1	2.1 ± 0.2	3.3 ± 1.0	
n cases/person-years	128/17298	135/17,253	123/17,261	128/17,155	
Multiple-adjusted model	1.00 (ref)	1.12 (0.88, 1.44)	1.04 (0.80, 1.35)	1.09 (0.82, 1.44)	0.72
Galacto-oligosaccharides					
Median, g/d	0.1	0.2	0.4	0.5	
Galacto-oligosaccharides, g/d	0.1 ± 0.1	0.2 ± 0.1	0.4 ± 0.1	0.6 ± 0.2	
n cases/person-years	131/17,174	133/17,204	125/17,155	125/17,435	
Multiple-adjusted model	1.00 (ref)	1.01 (0.80, 1.29)	0.97 (0.76, 1.24)	0.90 (0.69, 1.17)	0.41
Total prebiotics[3]					
Median, g/d	1.1	1.8	2.4	3.4	
Total prebiotics, g/d	1.1 ± 0.3	1.8 ± 0.2	2.4 ± 0.2	3.7 ± 1.0	
n cases/person-years	125/16,213	132/17,307	121/17,255	136/18,192	
Multiple-adjusted model	1.00 (ref)	1.04 (0.81, 1.34)	0.99 (0.76, 1.29)	1.03 (0.78, 1.36)	0.93
Men					
n	1485	1485	1485	1485	
Fructans					
Median, g/d	0.9	1.4	1.9	2.8	
Fructans, g/d	0.9 ± 0.2	1.4 ± 0.1	1.9 ± 0.2	3.1 ± 0.9	
n cases/person-years	52/12,156	49/12,241	69/12,348	43/12,203	
Multiple-adjusted model	1.00 (ref)	0.83 (0.56, 1.25)	1.16 (0.79, 1.71)	0.66 (0.42, 1.05)	0.24
Galacto-oligosaccharides					
Median, g/d	0.1	0.2	0.4	0.5	
Galacto-oligosaccharides, g/d	0.1 ± 0.1	0.2 ± 0.1	0.38 ± 0.1	0.62 ± 0.2	
n cases/person-years	56/12,046	54/12,221	47/12,260	56/12,421	
Multiple-adjusted model	1.00 (ref)	0.86 (0.59, 1.25)	0.74 (0.49, 1.12)	0.79 (0.52, 1.20)	0.24
Total prebiotics[3]					
Median, g/d	1.1	1.8	2.4	3.4	
Total prebiotics, g/d	1.1 ± 0.3	1.8 ± 0.2	2.4 ± 0.2	3.7 ± 1.0	
n cases/person-years	57/13,324	61/12,136	52/12,268	43/11,220	
Multiple-adjusted model	1.00 (ref)	1.07 (0.73, 1.56)	0.88 (0.59, 1.30)	0.71 (0.45, 1.11)	0.08

[1] Values were derived by using Cox regression analysis and repeated measurements of diet with baseline intake and updated dietary values from the FFQ after 10 y of follow-up (10-y follow-up questionnaire). The multiple-adjusted model adjusted for age (underlying time variable), sex, smoking (never, current, or former), physical activity (quartiles), total energy intake (quartiles), baseline BMI (quartiles), living alone, unemployment, marital status, and personality traits (competitive, relaxed, or dependent). Models were stratified by date of recruitment (2-y periods) and deciles of age. ref, reference; SUN, Seguimiento Universidad de Navarra.

[2] Mean ± SD (all such values).

[3] Total prebiotic consumption was the sum of galacto-oligosaccharides and fructans.

TABLE 3 HRs (95% CIs) for incident depression (diagnosis of depression) according to the consumption of yogurt in the SUN cohort (1999–2012) stratified by sex[1]

	Yogurt consumption[2]				
	<0.5 servings/wk (<63 g/wk)	≥0.5 to <3 servings/wk (≥63 to <250 g/wk)	≥3 to <7 servings/wk (≥250 to <875 g/wk)	≥7 servings/wk (≥875 g/wk)	*P*-trend
Overall sample					
Total yogurt					
Median	0	1	3	7	
n	3133	1,871	5,489	4046	
n cases/person-years	147/24,973	93/15,300	287/44,556	200/33,086	
Multiple-adjusted model	1.00 (ref)	1.02 (0.79, 1.31)	1.09 (0.90, 1.33)	1.00 (0.81, 1.25)	0.83
Whole-fat yogurt					
Median	0	1	3	7	
n	6445	1586	4091	2417	
n cases/person-years	347/52,103	76/12951	193/33,100	111/19,760	
Multiple-adjusted model	1.00 (ref)	0.86 (0.67, 1.10)	0.87 (0.73, 1.03)	0.78 (0.63, 0.98)	0.020
Low-fat yogurt					
Median	0	1	3	7	
n	9376	1034	2413	1716	
n cases/person-years	422/75,959	62/8320	144/19,690	99/13,946	
Multiple-adjusted model	1.00 (ref)	1.39 (1.08, 1.80)	1.32 (1.09, 1.58)	1.32 (1.06, 1.65)	0.001
Women					
Total yogurt					
Median	0	1	3	7	
n	1605	1057	3274	2663	
n cases/person-years	93/12,697	69/8363	210/26,218	142/21,690	
Multiple-adjusted model	1.00 (ref)	1.14 (0.84, 1.54)	1.15 (0.91, 1.46)	0.96 (0.74, 1.25)	0.75
Whole-fat yogurt					
Median	0	1	3	7	
n	3919	904	2300	1,476	
n cases/person-years	254/31,212	53/7219	137/18,524	70/12012	
Multiple-adjusted model	1.00 (ref)	0.86 (0.64, 1.15)	0.87 (0.71, 1.07)	0.66 (0.50, 0.87)	0.004
Low-fat yogurt					
Median	0	1	3	7	
n	4982	682	1659	1276	
n cases/person-years	263/40,011	53/5306	119/13,296	79/10,354	
Multiple-adjusted model	1.00 (ref)	1.72 (1.29, 2.29)	1.49 (1.20, 1.84)	1.37 (1.07, 1.76)	<0.001
Men					
Total yogurt					
Median	0	1	3	7	
n	1528	814	2215	1383	
n cases/person-years	54/12,276	24/6937	77/18,338	58/11,396	
Multiple-adjusted model	1.00 (ref)	0.80 (0.49, 1.29)	0.98 (0.68, 1.40)	1.22 (0.84, 1.78)	0.28
Whole-fat yogurt					
Median	0	1	3	7	
n	2526	682	1791	941	
n cases/person-years	93/20,892	23/5732	56/14,576	41/7748	
Multiple-adjusted model	1.00 (ref)	0.87 (0.55, 1.37)	0.85 (0.60, 1.19)	1.15 (0.79, 1.66)	0.86
Low-fat yogurt					
Median	0	1	3	7	
n	4394	352	754	440	
n cases/person-years	159/35,948	9/3014	25/6394	20/3592	
Multiple-adjusted model	1.00 (ref)	0.70 (0.36, 1.36)	0.90 (0.59, 1.38)	1.42 (0.89, 2.27)	0.53

[1] Values were derived by using Cox regression analysis and repeated measurements of diet with baseline intake and updated dietary values from the FFQ after 10 y of follow-up (10-y follow-up questionnaire). The multiple-adjusted model adjusted for age (underlying time variable), sex, smoking (never, current, or former), physical activity (quartiles), total energy intake (quartiles), baseline BMI (quartiles), living alone, unemployment, marital status, and personality traits (competitive, relaxed, or dependent). Models were stratified by date of recruitment (2-y periods) and deciles of age. ref, reference; SUN, Seguimiento Universidad de Navarra.
[2] 1 serving = 125 g.

(i.e., "hidden") cases of depression at baseline might be responsible for the higher low-fat yogurt consumption among participants who were diagnosed with depression early in the follow-up of the cohort. In fact, 1725 of the 2085 participants with prevalent depression consumed yogurt in our cohort.

Our finding of an inverse association between whole-fat yogurt consumption and depression is consistent with previous studies (41, 42). A cross-sectional study in 1745 pregnant Japanese women showed an association between a higher intake of yogurt and a lower prevalence of depressive symptoms during pregnancy (41). A fermented milk product with probiotics might positively affect the activity of brain regions that control central processing of emotion and sensation in healthy women (42). Furthermore, yogurt consumption has been related to a lower risk of overweight or obesity and metabolic syndrome (13, 14), diseases that have been previously related to depression (43). Moreover, preclinical research in rodents suggested that probiotics produce antidepressant and anxiolytic effects by beneficially affecting neural systems (noradrenaline) and normalizing corticosterone release and concentrations of inflammatory biomarkers (44, 45).

An association between the gut microbiota and depression has been found in humans (46), and an increase in beneficial bacteria and a reduction in potentially pathogenic bacteria have been observed after the consumption of commercial yogurt supplemented with probiotics in healthy adults (47). A human study showed that the status of the gut microbiota of mothers may have important repercussions for the mental and neurodevelopmental health of their children (48). Several studies have reported that $>1 \times 10^7$ CFUs $\cdot$ g^{-1} $\cdot$ d^{-1} (9) or 1×10^9 CFUs $\cdot$ serving^{-1} $\cdot$ d^{-1} (49) are enough to produce health benefits. Therefore, if a yogurt contains $\geq 1 \times 10^7$ CFUs/g, the consumption of 1 serving of yogurt (125 g)/d would be necessary to produce the health benefit. We acknowledge that probiotics have a transient effect on the gut microbiota. As stated by the International Scientific Association for Probiotics and Prebiotics, most probiotics should be consumed daily for obtaining their expected health benefit. In addition, further research is needed in the field of yogurt consumption and changes in gut microbiota because it is still necessary to clarify which bacterial populations are involved in depression (50), although studies with *Bifidobacterium infantis* show promising results (51).

The current study showed opposite results for the association of whole- and low-fat yogurt consumption with the incidence of depression. This explained why total yogurt consumption was not related to depression risk. Because whole- and low-fat yogurts seem not to differ in bacterial concentration (52), the probiotic hypothesis does not appear to fully explain the opposite associations found between whole- and low-fat yogurt consumption and depression risk in our results, although it may support the inverse association observed between whole-fat yogurt and depression. Together with beneficial bacteria, yogurt also contains zinc, vitamins (riboflavin, vitamin A, vitamin E, thiamine, vitamin B-6, and folate), protein, carbohydrates (lactose, glucose, and galactose), fat (including CLA), and minerals (calcium, magnesium, and potassium). However, the nutritional composition of yogurt varies depending on the species and strains of bacteria used in the fermentation, the type of milk (whole, semi-skim, or skim), fortification methods, store conditions, etc. (15, 53). CLA has been proposed to have gut anti-inflammatory properties (54), which may, in turn, improve immune activity (15). Depression has been related to low-grade inflammation, as well as with low folate consumption (34, 35). Whole-fat yogurt contains a higher amount of fat (which includes CLA) and folate than does fat-free yogurt (53). This hypothesis may contribute, at least in part, to explain why we only observed an inverse association for whole-fat yogurt consumption but not for low-fat yogurt.

The inverse association between whole-fat yogurt consumption and depression risk was significant only in women, although no significant interaction between whole-fat yogurt and sex was found. We may hypothesize that these differences are because, in general, women are more conscious of their diet (55) and this may lead to a lower measurement error in this group. Moreover, women are more likely to suffer from depression than men (56).

The current study has some strengths and limitations. Strengths of this study include its prospective longitudinal design, the use of previously validated methods (25), the large sample size, and the repeated measurements of diet. Participants were highly educated, which increases the quality of self-reported information and reduces the potential for misclassification bias. In addition, the restriction to a fairly homogenous subgroup of participants with regard to educational level minimizes the potential for residual confounding and is an excellent technique to improve the internal validity of our results. In addition, the long-term follow-up may reduce the potential for reverse causation bias.

A limitation of this study is that dietary intake and clinical diagnosis of depression were self-reported; however, both methods have been previously validated in our cohort (26, 27). Although our FFQ asks about the consumption of low- or whole-fat yogurt, it does not differentiate among other yogurt varieties (e.g., bio- or probiotic yogurt). Together with fructans and GOSs, other prebiotic sources should be acknowledged, but they were not included in the analysis because there are currently not enough data available in the literature (22). Moreover, our FFQ is composed of 136 items and information on some possible foods that contain prebiotics was not collected. We assumed a relatively long induction period (from 0 to 10 y) for the association of diet and depression. This may potentially be a strong assumption. However, dietary habits tend to be correlated within individuals across years of follow-up. Although 10 y was the longest possible follow-up period, most cases occurred after a follow-up period that was considerably shorter than 10 y. Although the follow-up questionnaires were mainly focused on outcomes (disease incidence, including depression incidence) and were completed every 2 y, the full-length FFQ was administered twice, at baseline and after 10 y of follow-up, which allowed the use of updated information on diet after 10 y. Another potential limitation is that our participants are university graduates and research in other population groups is needed before our findings can be extrapolated to the general population. Finally, it would have been of interest to determine the gut microbiota composition of the participants, but stool samples were not available in this study.

In summary, a high consumption of whole-fat yogurt was related to a lower risk of depression in women of the SUN cohort. The consumption of prebiotics was not significantly associated with depression risk. The different effect observed depending on the fat content of the yogurt encourages further prospective studies to clarify these matters.

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AP-C, MB-R, and MAM-G designed the research; AP-C conducted the research, analyzed the data, performed statistical analysis, and wrote the manuscript; AS-V, AG, PM, and FL-R provided essential materials; MB-R, FL-R, and MAM-G were responsible for administrative support and funding; AP-C and MAM-G had primary responsibility for the final content. All authors revised the manuscript for important intellectual content and read and approved the final manuscript.

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